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MODERN CONCEPTS OF ANEMIA FROM THE CLINICAL STANDPOINT*

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In the past two decades hematologists—whether in the laboratory or in practice, and especially in this country—have become increasingly aware of the benefits of studying the blood from functional, chemical and metabolic standpoints as well as from purely morphologic. The cell type period that started with the differential stains of Ehrlich and reached its climax in Europe with Pappenheim and Ferrata had finished its major contribution and was concerned with wearisome subdivisions of cell types that often proved to be either wrong or of minor significance. The opposing schools of the monophyletic and polyphyletic origin of the different blood cells have far from settled their differences and while it is of course desirable, yes even essential, that eventually the origin of each blood cell be definitely settled, yet we have become increasingly efficient in preventing this gap in our knowledge from holding up progress in other lines of hematologic research.

One such approach emphasizes the dynamic aspect of the peripheral blood and the blood-cell forming tissues as an exquisitely balanced, constantly active mechanism which demands, perhaps to our occasional sorrow, that we study the condition of the tissue as well as the blood

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itself in order to understand the present state of the system. How much has the study of blood diseases suffered from not having a convenient label such as "heart," or "kidney," or even "reticuloendothelial system" to indicate the unity of the two parts! The term "erythron" has been suggested as such a label for the red cell portion of the system but is not widely used in this country. Admitting that the bone marrow is a difficult tissue to study, still it would no longer be wise in this country to assert, as Turck was said to have done when asked about the bone marrow, "Sir, I am a peripheral hematologist!" No longer can we be content with the static information furnished by routine hospital request, for "reds, whites, hemoglobin, and differential;" but if there is a disturbance in what I some years ago called the "hemolytopoietic equilibrium," the balance between the cell formation and destructive tendencies, we must seek evidence as to whether the disturbance is due to increased blood cell loss or destruction or decreased formation; and if the latter, whether the inefficient formation is due to lack of hemoglobin-building material; or of stroma-building material; or both; or of some regulatory substance that prevents either normal maturation of the cell in the factory, or expulsion of the fully formed cell into the circulation.

One of the developments of the dynamic viewpoint is the increasing use of sternal puncture, now a relatively trivial procedure under local anesthesia, which may once or even repeatedly give diagnostic and prognostic information about a given "blood" case that is not obtainable in any other way. There are now several good booklets and medical articles on this subject in English which will give you the information that I have not time to include here. Spreads from the puncture on slides may be made to identify cell types; or better, paraffin sections prepared which also show proportions and relations. Splenic puncture is another procedure that is routinely practised in certain parts of Europe, allegedly with profit to patient as well as doctor and without harm. It has not been tried enough in this country to warrant even a cautious recom-

mendation but it would not be surprising to see it also being used by us in another decade.

What then do we need for a reasonable study of the peripheral blood of a given case of anemia? Erythrocyte and hemoglobin estimations and a stained spread remain most important, though the hemoglobin should be given in grams rather than in per cent of an unknown and arbitrarily fixed normal. Also repeated counts, not foolishly often, are important in establishing a prognostic curve, especially if normal levels have previously been recorded. From this material the color index can be estimated and measurements of erythrocyte diameters made, either directly by an ocular micrometer, or projected on a wall, to give a Price-Jones curve or an average diameter —normal about 7.2 - 7.8 micra—obtained with an "Eriometer." This depends on the principle discovered a century ago by Young that a spectral ring will vary in size with the size of the round bodies that light is passed through. Of course evidence of regenerative ability is furnished by the number and type of nucleated reds and the amount of polychromatophilia. More accurate for the non-nucleated young erythrocytes, however, is estimation in a vital stain, such as brilliant cresyl blue, of the per cent of the cell which, in 1922, I named the "reticulocyte" a name which was popularized by the use Minot made of it in determining regression in pernicious anemia. A simply determined hematocrit test under standard conditions gives the per cent of the collective volume of packed blood cells in a blood sample. The "Mean Corpuscular Volume" is determined by the number of total cubic micra in the hematocrit cells divided by the number of cells per cu. mm.; or the reading times ten over the number of million red blood cells. This is normally about 80 to 90 cubic micra, a more sensitive and more logical estimation of size than measurement of erythrocyte diameter. Various other calculations can be made to furnish volume indices, corpuscular hemoglobin content, and concentration, but are of less practical value.

As you all know, Minot and Murphy made the dramatic discovery in 1926 that pernicious anemia, hitherto a hopelessly incurable disease, could be regularly cured by liver extract, in the sense that proper treatment could not only check the disease but keep the patient in good health as long as treatment was continued. This not only was in itself a major medical discovery of the century which already has saved thousands of lives, but has also proved to be instrumental in changing our concepts of anemia in general. No longer do we airily divide cases into the "primary and secondary anemias," even though "primary" meant little more than "of unknown origin" and though "secondary" was practically regarded as a single disease group instead of the many groups which really were different in their nature and manifestations and required different remedial therapy.

To-day we know a number of conditions causing a "macrocytic" form of anemia, a "microcytic," and a "normocytic," though we may be still groping for the common factor that produces the picture. This has not only completely disposed of the former German classification of pernicious anemia into idiopathic and secondary forms but has provided a most useful generalization for treatment, namely, that liver extract is apt to be the best treatment for all anemias associated with macrocytosis. In the same way we have come to associate an acquired microcytosis, especially if hypochromic, with nutritional deficiencies, and especially with a lack of available iron; so that sufficient iron therapy, in whatever form it may be given, is practically a specific for these types.

For an orderly consideration of anemias, we must have a classification, though to-day's best may easily be replaced by a better one to-morrow. As our knowledge is not yet sufficiently advanced to make a strictly etiological classification desirable, setting aside the "primary" and "secondary," it seems best to consider a pathogenetic classification something like that of Table 1.

TABLE 1.

A CLASSIFICATION OF ANEMIAS

I. Mainly due to Disorders of Erythrocyte Formation:

(a) Insufficient formation in bone marrow, usually normocytic (*aplastic, myelophthisic, due to physical injury, etc.*)

(b) Defective formation:

1. Erythroblastosis.
2. Spherocytic (*hemolytic jaundice*).
3. Ovalocytic.
4. Sickle cell anemia.
5. Poikilocytic, normochromic or hypochromic* (*deficiency of diet, vitamin* or *hormone, hookworm, chlorosis, "idiopathic,"* etc.)
6. Macrocytic* (*pernicious, sprue, pellagra, secondary to some gastro-intestinal or liver disorders,* etc.)

II. Mainly due to Blood Loss:

(a) Hemorrhage from trauma (*acute blood loss*).

(b) Chronic or intermittent bleeding, as in gastro-intestinal and genito-urinary tract.

(c) Abnormal blood vessels or other blood constituents (*purpura, hemophilia*).

III. Mainly due to Excessive Destruction:

(a) Hemolytic infections, toxins, poisons, etc.

(b) Secondary to defective formation (*see Ib*).

(c) Unknown nature (*Lederer's*) (*Banti's*).

It is obvious that some clinical pictures cannot be fitted exactly into such a category and that some, such as hemolytic jaundice, could as well be put in the class of excessive blood destruction as defective formation, if one chose to emphasize the result rather than the cause. Furthermore, we have found that even such a simple type as traumatic hemorrhage, for example, may produce a macro-, normo-, or microcytic type of anemia, depending on the intensity, and duration of the hemorrhage. For such reasons a classification based purely on size of cells seems undesirable at the moment.

Using such a tentative classification, I shall discuss briefly the different types.

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* Anemia of pregnancy and of celiac disease may occur either as macrocytic or hypochromic, depending on what element is chiefly lacking.

Aplastic Anemia. This marrow insufficiency, as you know, may be caused by a number of chemical poisons, such as arsenic, bismuth, or benzol; by physical agents, such as X-ray or radium; by some overwhelming infections; or by a terminal exhaustion of the bone marrow in pernicious anemia, leukemias, other severe anemias and even in polycythemia. Also we still have to include the "Idiopathic" types, i.e., those in which the cause is still entirely unknown. Though some of these causes frequently depress the leukocyte forming centres, they may also attack the red cell centres or all three, i.e., megakaryocytes.

In the complete form we recognize no regenerative signs either in the bone marrow or in the peripheral blood. However, we must also recognize forms in which, with no signs of regeneration in the blood stream, a relatively hyperplastic bone marrow is found (loss of expelling stimulus?) ; or in which more immature red cells are found in the circulation than bone marrow study would suggest. Of course, the different levels of activity of different bone marrows must here be taken into account in forming an estimate of aplasia. A tibial marrow might show aplasia, for instance, when femoral showed considerable regenerative activity, or femoral be fatty when sternum or vertebra was active.

Another rarely recognized condition is Cooley's *Erythroblastosis* of children, also called "icterus gravis" and "hydrops universalis." This produces a marked anemia in spite of the excessive signs of blood cell formation in bone marrow, liver, and spleen, because of the congenital defectiveness of the red cells that are formed. The racial element, especially its predilection for the peoples of the Mediterranean littoral; familial incidence; the presence of many nucleated red cells in the blood; splenomegaly, not helped by splenectomy, are associated features which may permit this condition to be differentiated from other puzzling anemias of childhood. This disease undoubtedly is often confused with v. Jaksch's anemia, a term which probably should be further dissected till nothing is left.

Congenital and Acquired Hemolytic Jaundice. It is now recognized that the most important feature in this disease is that the small red cells tend to be more spherical than normal and that therefore they rupture more easily in hypotonic salt solution. This is the well known "increased fragility" phenomenon. This is often but one of several anomalies that the individual may exhibit, such as, tower skull, bone and tooth defects, and is presumably the prime fault. In fact, "acquired hemolytic jaundice" is now believed to represent latent cases of the congenital disease brought to the level of clinical prominence by the addition of some other condition, such as syphilis or gall bladder trouble. Splenectomy continues to be the treatment of choice, though a recent suggestion that it may even be performed during a crisis, i.e., without waiting for a remission or the beneficial effects of transfusion, is one that should be followed with caution and reluctance. Though splenectomy is usually followed by clinical cure, the resistance of the red blood cells seldom returns all the way to normal; another fact in favor of the view that the prime fault lies in a congenital defect of the red blood cell.

Just as congenital hemolytic jaundice may remain latent in some instances, so in sickle cell anemia we have to recognize that many persons with this condition are not anemic, i.e., sicklemia, but are more liable to become so with any strain on the red cell system than persons with normal erythrocytes. An increasing number of established diagnoses of this condition in persons in whom negro blood can reasonably be excluded shows that we must revise our concept of sicklemia as one occurring solely in negroes. The extremely small size of the spleen in these cases still remains a mystery.

The elliptical erythrocytes should not be confused with sickle cells. They do not show the same tendency to increase when the blood stands outside the body, nor do they show preference for negroes and are never associated with severe anemia.

Turning to much more common and therefore important conditions, let us consider the various anemias associated especially with lack of hemoglobin, hypochromic anemias, which of course give a low color index. On the stained smear the corpuscles are recognizably paler, show great variations in size, and are often distorted in shape. Not only is the mean volume of the red blood cell reduced, but also the hemoglobin concentration of each. This gives a clue to the nature of the disorder, which is a greater deficiency of iron than of stroma, according to current concepts; and also suggests the treatment, as iron is practically a specific. If iron in sufficient quantities fails to give relief, sometimes the addition of a small amount of copper will benefit, although the reason for this is not clear.

Such anemias occur from long continued hemorrhages, such as menorrhagia, oozing piles, gastro-intestinal ulcers, hookworm; from improper diet, especially if deficient in iron; after total gastrectomy; in a gastro-intestinal state preventing absorption; and from the excessive demands for iron in pregnancy. In all these the sequence leading to an iron deficiency is apparent. It is noteworthy that the first group may also produce a macrocytic type of anemia that is in some respect similar to pernicious anemia, an indication of the limitations of a classification based on the size of the red cell. In pregnancy also both the hypochromic and hyperchromic or macrocytic forms of anemia may be encountered, the latter still called the pernicious anemia of pregnancy. If the mother has not taken in enough iron for both self and fetus, the hypochromic form of anemia results and is best treated by iron; if her gastric intrinsic factor is insufficient, according to Castle's concept, or if not enough of the extrinsic factor be taken in the diet, the macrocytic form appears. It is best treated by liver extract.

Where the cause cannot be found, the term "idiopathic hypochromic anemia," must be used, though it is an admission of ignorance. The relation of this to "chlorosis"

is not clear. This once common diagnosis is now relatively rare. Few modern studies of blood and bone marrow have been made on it. Perhaps it may be included in some of the categories already mentioned.

In some cases of the old "secondary anemia," stroma and hemoglobin are reduced in equal measure, leaving an isochromic state. Such "simple chronic anemia" may be found in any of the infections or toxic states that are of sufficient intensity or duration, or in chronic nephritis, or malignancy.

The most important group of all to consider is that associated with "hyperchromic or macrocytic anemia,"—as it is now called, in which the hemoglobin formation is less at fault than other factors, such as the maturation defect that is known to be remedied by liver extract, and perhaps other still dimly envisaged factors, such as stroma formation or one leading to prompt division of the new forming cells.

As you may well realize, one of the superlative merits of Minot's discovery of the potency of liver extract was that it not only produced a means of curing a hitherto incurable disease but also started a productive line of study of a whole group of anemias which is still far from being exhausted.

We already know that conditions other than pernicious anemia may produce macrocytosis. If we accept Castle's view that adequate anti-anemic substance, formed from his extrinsic and intrinsic factors, is necessary for the maturation of normal red blood cells; then anything interfering with this adequacy will give a macrocytic anemia. Other factors such as infection, toxin, altered metabolism are secondary. How may we apply this to our macrocytic anemias? In pernicious anemia there is little if any intrinsic factor present. When it is supplied in the form of liver, or liver extract, a remission promptly follows. The anemia of sprue responds either to liver extract or to autolyzed yeast, indicating that here it is the extrinsic factor that is lacking and the same usually holds for the

macrocytic anemia of pregnancy. In the microcytic, hypochromic anemia of pregnancy, on the other hand, there is an iron deficiency due either to the deficient diet or to the extra iron demands of the fetus, and this is promptly relieved by administration of adequate amounts of iron. There is also evidence that an inability to absorb the anti-anemic substance may be responsible for the macrocytic anemia. This mechanism seems to be at least a factor in the macrocytic anemia of celiac disease, idiopathic steatorrhea, long continued tropical diarrhea, sprue, and in some post-operative gastro-intestinal resections and short cuts. While the occasional macrocytic anemia of diphyllobothriasis (fish tape-worm) has not been definitely explained, it is probable that it also is mainly due to dietary irregularities interfering with the formation of the "anti-anemic substance." In pellagra, also, with the frequent presence of inadequate diet and chronic alcoholism, nutritional deficiency is probably to blame for the anemia. This is reenforced by the knowledge, that liver extract will arrest the progress of neural lesions in pernicious anemia, and vitamin B will do the same in pellagra.

I have not reached the end of my classification but remaining categories less strikingly support the point of view that I have been trying to emphasize. The etiology of acute or chronic blood loss is clear in theory but we are quite in the dark as to why different degrees of acute blood loss, or different duration and intensity of chronic loss, may produce different types of anemia. Experimentally we have found that either macro- or micro-cytic anemia can be produced by altering these factors. We can only speculate as to the relative depletion of materials forming hemoglobin, or stroma, or governing maturation or expulsion; but already it is prudent to regulate therapeutic measures according to the type of anemia found. The same holds true for the large group of anemias due to increased blood destruction, whether from extrinsic or intrinsic causes. We must admit, however, deficiencies in our knowledge of such common conditions as the anemia of Bright's disease, and cancer. The variation in the

clinical picture appears to be due in many instances to a preponderance of different factors in different persons suffering from the same disease. Our own studies on renal anemia indicate that defective blood formation plays the predominant role. In cancer it is obvious that in some cases, hemorrhage, in other cases deficient nutrition predominate; while the question of a specific cancer toxin remains unanswered.

While the gaps in our hematologic knowledge are thus only too apparent, I have sought to give some indication of progress that has recently been made in the study of the anemias, and of the desirability of regarding them from the dynamic standpoint of disturbances in the exquisite balance of the various parts of the "erythron."